

Integrase Inhibitor-based regimens: Abacavir/dolutegravir/lamivudine (Triumeq) and Elvitegravir (Vitekta)

Abbreviated Drug Monograph

June 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹⁻²

Description/Mechanism of Action

Abacavir/dolutegravir/lamivudine: Fixed-dose combination of Integrase Inhibitor and two Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Of note, each of the individual components of this product along with the combination of abacavir/lamivudine has previously been approved by the FDA. **Elvitegravir:** Single agent Integrase Inhibitor. The FDA had previously approved elvitegravir as part of elvitegravir/cobicistat/emtricitabine/tenofovir quadruple combination product.

Indication(s) Under Review in this document (may include off label)

Abacavir/dolutegravir/lamivudine is indicated for the treatment of human immunodeficiency virus (HIV)-1 infection.

Limitations of Use:

- Abacavir/dolutegravir/lamivudine alone is not recommended in patients with current or past history of resistance to any component of abacavir/dolutegravir/lamivudine.
- Abacavir/dolutegravir/lamivudine alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance. The dose of dolutegravir in this formulation is insufficient in these subpopulations. Refer to dolutegravir monograph for further information.

Elvitegravir is indicated for use with an HIV protease inhibitor coadministered with ritonavir and another antiretroviral agent for the treatment of HIV-1 infection in treatment-experienced adults.

Limitations of Use:

- There are no comparative pharmacokinetic or clinical data evaluating elvitegravir with cobicistat as single entities compared to elvitegravir/cobicistat/emtricitabine/tenofovir.
- Elvitegravir coadministered with protease inhibitors and cobicistat is not recommended.
- Coadministration of elvitegravir with dosage regimens or HIV-1 protease inhibitors other than those presented in Dosage Administration section is not recommended.

Dosage Form(s) Under Review

Abacavir/ dolutegravir/lamivudine 600mg/50mg/300mg tablet
Elvitegravir 85mg and 150 mg tablets

REMS

☐ REMS ☒ No REMS ☐ Postmarketing Requirement

Pregnancy Rating

Abacavir/dolutegravir/lamivudine: Category C
Elvitegravir: Category B

Executive Summary¹⁻⁶

Efficacy

Abacavir/ dolutegravir/lamivudine

- Approval of abacavir/dolutegravir/lamivudine was primarily based on two Phase 3 trials (SINGLE and SAILING) conducted for the approval of dolutegravir formulated as a single agent. SINGLE trial was conducted in adult patients who were antiretroviral-treatment naïve while SAILING trial was conducted in treatment-experienced patients. Both were randomized, multicenter, double-blind, active-controlled trials.
- The primary efficacy endpoint in the SINGLE trial compared the proportion of

	<p>patients with an undetectable HIV-1 viral load at 48 weeks of dolutegravir in combination with abacavir/lamivudine compared to efavirenz/tenofovir/emtricitabine. Dolutegravir-containing regimen was found to be superior in 80% v. 72%, respectively at 96 weeks (95% CI 2.3 to 13.8).</p> <ul style="list-style-type: none"> The primary efficacy endpoint in the SAILING trial compared the proportion of patients with an undetectable HIV-1 viral load at 48 weeks of dolutegravir in combination with two active antiretrovirals compared to raltegravir in combination with two active antiretrovirals [71% v. 64%, respectively at 48 weeks (95% CI 0.7 to 14)]. <p>Elvitegravir</p> <ul style="list-style-type: none"> Approval of elvitegravir was primarily based on one randomized, multi-center, Phase 3 trial evaluating adult patients who were treatment-experienced. The primary efficacy endpoint was the proportion of patients with HIV-1 viral load <50 copies/mL at 96 weeks; the two regimens compared were elvitegravir in combination with ritonavir boosted protease inhibitor plus another antiretroviral and raltegravir co-administered with ritonavir boosted protease inhibitor plus another antiretroviral. The pre-specified 10% non-inferiority margin was met, 52% v. 53%, respectively.
Safety	<p>Abacavir/dolutegravir/lamivudine</p> <ul style="list-style-type: none"> Common adverse events observed for dolutegravir in combination with abacavir/lamivudine were insomnia, headache, and fatigue. Boxed warning exists for serious and sometimes fatal hypersensitivity reactions been associated with abacavir-containing products. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Boxed warning also for lactic acidosis and severe hepatomegaly with use of nucleosides as well as exacerbations of hepatitis B if lamivudine discontinued in patients co-infected with hepatitis B and HIV. <p>Elvitegravir</p> <ul style="list-style-type: none"> Common adverse events observed for elvitegravir were diarrhea, nausea, and headache.
Potential Impact	<p>Abacavir/dolutegravir/lamivudine</p> <ul style="list-style-type: none"> Abacavir/dolutegravir/lamivudine is available as a fixed-dose one tablet once daily regimen. It is FDA approved for the treatment of HIV-1 infections and is a DHHS recommended regimen for antiretroviral-naïve patients. <p>Elvitegravir</p> <ul style="list-style-type: none"> Elvitegravir is approved for use in treatment-experienced HIV-1 infections in combination with a ritonavir boosted HIV protease inhibitor and a second antiretroviral drug.

Background

Purpose for review

Recent FDA approvals: Abacavir/dolutegravir/lamivudine (August 22, 2014) and Elvitegravir (September 24, 2014)

Issues to be determined:

- ✓ Evidence of need
- ✓ Do abacavir/dolutegravir/lamivudine and elvitegravir offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives for HIV Integrase Inhibitors	Other Considerations
Raltegravir	-BID dosing
Dolutegravir	-QD or BID dosing for certain treatment-experienced patients
Elvitegravir/cobicistat/emtricitabine/tenofovir	-Fixed dose combination (1 tab QD)

-Not recommended in patients with CrCl <70 mL/min

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to April 2015) using the search terms <Elvitegravir>, <Vitekta>, <Dolutegravir>, <Prezcobix>. The search was limited to studies performed in humans and published in the English language. Key randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy³⁻⁵

Abacavir/ dolutegravir/lamivudine: The FDA indication for abacavir/dolutegravir/lamivudine was primarily based on two Phase 3 trials conducted for the approval of dolutegravir formulated as a single agent (Table 1). These trials were conducted predominantly in Europe, Australia, and North America. The study populations were primarily male and white. Please refer to the full dolutegravir drug monograph for more clinical trial details (available at www.pbm.va.gov).

Table 1: Clinical Trials Supporting Abacavir/dolutegravir/lamivudine FDA Indications and Results

Clinical Trials	Study	Population	Regimen	Results	Primary Efficacy Endpoint Results
Phase 3	ING114467 (SINGLE)	Treatment-naïve	Dolutegravir + ABC/3TC (n=414) compared to EFV/TDF/FTC (n=419)	Dolutegravir with ABC/3TC was found to be superior to EFV/TDF/FTC	Proportion of patients with HIV-1 viral load <50 copies/mL at 96 weeks: Dolutegravir 80% vs EFV/TDF/FTC 72% (95% CI 2.3 to 13.8)
Phase 3	ING111762 (SAILING)	Treatment-experienced, integrase inhibitor naïve	Dolutegravir with one or two active ARV's as background therapy compared to raltegravir with one or two active ARV's as background therapy	Dolutegravir with other ARV background therapy was superior to raltegravir with other ARV background therapy	Proportion of patients with HIV-1 viral load <50 copies/mL at 48 weeks: dolutegravir 71% (251/354) vs. raltegravir 64% (230/361) (95% CI 0.7 to 14)

Overall quality of evidence: High (Refer to Appendix A); please note that all trials were funded by ViiV Healthcare
ABC=abacavir; FTC=emtricitabine; 3TC=lamivudine; EFV=efavirenz; TDF=tenofovir ARV: antiretroviral

Elvitegravir: The FDA indication for elvitegravir was primarily based on one pivotal Phase 3 trial (Table 2). This trial was conducted at 234 sites in 13 countries. Overall, the study population was mostly male (82%) and white (62%).

Table 2: Clinical Trials Supporting Elvitegravir FDA Indications and Results

Clinical Trial	Study	Population	Regimen	Results	Primary Efficacy Endpoint Results
Phase 3	Study 145	Treatment-experienced, integrase inhibitor naïve	Elvitegravir compared to raltegravir both co-administered with ritonavir boosted protease inhibitor and a second antiretroviral drug	Elvitegravir was non-inferior to raltegravir when coadministered with ritonavir boosted protease inhibitor and a second antiretroviral drug	Proportion of patients with HIV-1 viral load <50 copies/mL at 96 weeks: Elvitegravir 52% (182/351) vs. raltegravir 53% (186/351) (95% CI -7.9 to 6.8)

Overall quality of evidence: Moderate (Refer to Appendix A); please note that trial was funded by Gilead Sciences

Potential Off-Label Use⁷

- Elvitegravir in combination with other antiretroviral agents for the treatment of HIV infection in treatment-naïve or treatment-experienced patients

Safety¹⁻⁵

(for more detailed information refer to the product package insert)

Comments

Boxed Warning	<ul style="list-style-type: none">• Abacavir/dolutegravir/lamivudine:<ul style="list-style-type: none">○ Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products.○ Hypersensitivity to abacavir is a multi-organ clinical syndrome.○ Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir.○ Discontinue as soon as hypersensitivity reaction is suspected and never restart abacavir-containing product following a hypersensitivity reaction to abacavir.○ Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues.○ Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus and HIV and have discontinued lamivudine.• Elvitegravir:<ul style="list-style-type: none">○ None
Contraindications	<ul style="list-style-type: none">• Abacavir/dolutegravir/lamivudine:<ul style="list-style-type: none">○ Presence of HLA-B*5701 allele○ Previous hypersensitivity reaction to abacavir, dolutegravir, or lamivudine○ Coadministration with dofetilide○ Moderate or severe hepatic impairment• Elvitegravir: None
Warnings/Precautions	<ul style="list-style-type: none">• Abacavir/dolutegravir/lamivudine:<ul style="list-style-type: none">○ Hypersensitivity reactions○ Lactic acidosis and severe hepatomegaly with steatosis○ Patients with Hepatitis B or C virus co-infection○ Use with interferon- and ribavirin-based regimens○ Immune reconstitution syndrome○ Fat redistribution○ Myocardial Infarction○ Administration of abacavir/dolutegravir/lamivudine is not recommended in patients receiving other products containing abacavir or lamivudine.• Elvitegravir:<ul style="list-style-type: none">○ Do not use with protease inhibitors coadministered with cobicistat.○ Do not use with other elvitegravir-containing drugs, including elvitegravir/cobicistat/emtricitabine/tenofovir.○ Immune reconstitution syndrome: May necessitate further evaluation and treatment.

Safety Considerations

Abacavir/dolutegravir/lamivudine: The safety assessment based upon data from two Phase 3 studies that include a combined total of 773 patients treated with dolutegravir co-administered with abacavir and lamivudine and 780 patients treated with comparator agents.

Elvitegravir: The safety assessment based upon data from one Phase 3 study that included 354 patients treated with elvitegravir.

Adverse Reactions

Common adverse reactions	<u>Incidence >2%</u> Abacavir/dolutegravir/lamivudine: Insomnia (3%), headache (2%), fatigue
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	(2%) Elvitegravir: Diarrhea (7%), nausea (4%), headache (3%)
Death/Serious adverse reactions	Abacavir/dolutegravir/lamivudine: There were 11 deaths observed in dolutegravir exposed subjects in Phase 2b and Phase 3 trials. The study investigators indicated that these deaths were not related to dolutegravir. Elvitegravir: There were 2 deaths observed in elvitegravir exposed subjects in a Phase 3 trial and were deemed unrelated to elvitegravir.
Discontinuations due to adverse reactions	Abacavir/dolutegravir/lamivudine: 3% (vs. 11% in comparator arm) Elvitegravir: 3% (vs. 4% in the comparator arm)

Drug Interactions

Drug-Drug Interactions¹⁻²

- Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gb. Drugs that induce those enzymes or transporters may decrease dolutegravir plasma concentrations while drugs that inhibit these enzymes may increase dolutegravir concentrations. Abacavir and lamivudine have no known metabolism or transport effects.
 - Co-administration of abacavir/dolutegravir/lamivudine with dofetilide is contraindicated
 - Co-administration of the following agents with dolutegravir/abacavir/lamivudine should be avoided: Nevirapine, oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St. John's wort.
 - Co-administration with fosamprenavir/ritonavir, tipranavir/ritonavir, efavirenz or rifampin requires an additional dolutegravir 50mg dose to be given 12 hours after abacavir/dolutegravir/lamivudine
 - Abacavir/dolutegravir/lamivudine should be taken 2 hours before or 6 hours after medications containing polyvalent cations (e.g., Mg, Al, Fe, or Ca) such as cation-containing antacids or laxatives, sucralate, oral iron supplements, oral calcium or buffered medications. Of note, the PI states abacavir/dolutegravir/lamivudine and supplements containing calcium or iron can be taken together with food.
 - Ethanol decreased elimination of abacavir causing an increase in overall exposure.
- Elvitegravir is primarily metabolized by CYP3A with some contribution from UGT1A1 and UGT1A3. Drugs that induce those enzymes may decrease elvitegravir plasma concentration while drugs that inhibit these enzymes may increase elvitegravir plasma concentration.
 - Co-administration of elvitegravir with cobisistat is not recommended because dosing recommendations for this combination have not been established outside of fixed combination elvitegravir/cobicistat/emtricitabine/tenofovir.
 - Co-administration of the following agents with elvitegravir should be avoided: Efavirenz, nevirapine, oxcarbazepine, phenytoin, phenobarbital, carbamazepine, rifampin, rifapentine, and St. John's wort
 - Co-administration of atazanavir/ritonavir or lopinavir/ritonavir requires dose adjustment of elvitegravir 85mg once daily.
 - Elvitegravir should be separated by at least 2 hours from medications containing polyvalent cations (e.g., Mg, Al, Fe, or Ca) such as cation-containing antacids or laxatives, sucralate, oral iron supplements, oral calcium or buffered medications based on pharmacokinetic studies.
- Table 3 is adapted from DHHS HIV guidelines that highlight some of the potential drug interactions for integrase inhibitors.

Table 3. Mechanisms of Potential Integrase Inhibitor Drug Interactions⁶

	Cationic chelation	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	Other mechanisms of drug interactions
Dolutegravir	Concentration decreased by products containing	Substrate	3A4 (small contribution)	Substrate	Inhibitor of renal transporters OCT2 and MATE

Elvitegravir	polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	...	3A4	Substrate	...
Raltegravir		Substrate	...

Please refer to the full prescribing information and the DHHS guidelines for additional information on drug-drug interactions and any dose adjustment recommendations.

Risk Evaluation

As of 4/3/2015

	Comments
Sentinel event advisories	<ul style="list-style-type: none"> Abacavir/dolutegravir/lamivudine: Development of clinically-suspected abacavir hypersensitivity reaction requires immediate and permanent discontinuation of abacavir therapy in all patients, including patients negative for HLA-B*5701 (FDA). Elvitegravir: None
Look-alike/sound-alike error potentials	<ul style="list-style-type: none"> Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First Databank	ISMP	Clinical Judgment
Abacavir-dolutegravir-lamivudine 600-50-300mg tab	None	None	None	Abacavir-lamivudine Abacavir-lamivudine-zidovudine Atazanavir
Triumeq	None	None	None	Trianex Treximet Trianex Trizivir Triaminic

NME Drug Name	Lexi-Comp	First Databank	ISMP	Clinical Judgment
Elvitegravir 85, 150mg tab	None	None	None	Entecavir Epivir Raltegravir Dolutegravir
Vitekta	None	None	None	Vidaza Viekira

Other Considerations⁶

The DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were most recently updated in April 2015. The DHHS Panel positions the following 4 INSTI-based regimens as “recommended” regimens for antiretroviral-naïve patients (arranged in alphabetic order):

- Raltegravir 400 mg twice daily plus tenofovir 300 mg/emtricitabine 200 mg once daily (AI)
- Elvitegravir 150 mg/cobicistat 150 mg/tenofovir 300 mg/emtricitabine 200 mg once daily in patients with estimated CrCl ≥ 70 mL/min (AI)
- Abacavir 600 mg/dolutegravir 50mg/lamivudine 300 mg once daily in patients who are HLA B*5701 negative (AI)
- Dolutegravir 50 mg once daily plus tenofovir 300 mg/emtricitabine 200mg once daily (AI)

In antiretroviral-experienced patients, the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents recommends a new antiretroviral regimen of at least two, and preferably three drugs with activity against drug-resistant viral strains. For more details, please refer to guidelines.

- In the presence of certain drug resistance mutations, dolutegravir must be given twice daily in order to achieve high enough drug concentrations.

The DHHS guidelines state that elvitegravir is “available as a single agent designed to be used in combination with PI/r in antiretroviral-experienced patients, and is not recommended for use in treatment-naïve patients.”

Dosing and Administration¹⁻²

Table 4: FDA Approved Abacavir/dolutegravir/lamivudine Dosing Recommendations

Adult Population	Recommended Abacavir/dolutegravir/lamivudine Dosage Regimen
Treatment-naïve or treatment-experienced Integrase Inhibitor naïve	Fixed-dose combination (600 mg/50 mg/300 mg) once daily
Co-administration with fosamprenavir/ritonavir, tipranavir/ritonavir, efavirenz or rifampin	Additional dose of dolutegravir 50 mg 12 hours after abacavir/dolutegravir/lamivudine fixed-dose combination

Elvitegravir must be administered once daily with food in combination with a protease inhibitor co-administered with ritonavir and another antiretroviral drug. The protease inhibitor and ritonavir dosing regimens presented in Table 5 are the recommended regimens for use with elvitegravir. Treatment history and resistance testing should guide the use of elvitegravir-containing regimens.

Table 5: FDA Approved Elvitegravir Dosing Recommendations

Adult Population	Recommended Elvitegravir Dosage Regimen
Concomitant with the following HIV Protease inhibitors: <ul style="list-style-type: none"> - Atazanavir 300 mg orally once daily with ritonavir 100 mg orally daily OR - Lopinavir/ritonavir 400 mg/100 mg orally twice daily 	85 mg orally once daily
Concomitant with the following Protease inhibitors: <ul style="list-style-type: none"> - Darunavir 600 mg orally twice daily with ritonavir 100 mg orally twice daily OR - Fosamprenavir 700 mg orally twice daily with ritonavir 100 mg orally twice daily OR - Tipranavir 500 mg orally twice daily with ritonavir 200 mg orally twice daily 	150 mg orally once daily

Special Populations (Adults)¹⁻²

	Comments
Elderly	<ul style="list-style-type: none"> • Clinical trials have not included sufficient number of subjects aged 65 and over. Caution should be used in the administration of abacavir/dolutegravir/lamivudine or elvitegravir in elderly as they are more likely to have decreased baseline renal function.
Pregnancy	<p>Abacavir/dolutegravir/lamivudine: Pregnancy Category C; Reproduction studies have only been performed with each drug component in animals. Weigh potential risks and benefits to infant and mother before use.</p> <p>Elvitegravir: Pregnancy Category B; Reproduction studies have only been performed in animals. Weigh potential risks and benefits to infant and mother before use.</p>
Lactation	<ul style="list-style-type: none"> • The CDC recommends that HIV-infected mothers not breastfeed their infant children to avoid risking postnatal transmission and the potential for serious adverse reactions in nursing infants.
Renal Impairment	<ul style="list-style-type: none"> • Abacavir/dolutegravir/lamivudine is not recommended for patients with CrCl < 50 mL/min. • Elvitegravir: There were no clinically relevant differences in pharmacokinetics observed in severe renal impairment and healthy

	subjects. No dose adjustments are required.
Hepatic Impairment	<ul style="list-style-type: none"> • Abacavir/dolutegravir/lamivudine is not recommended in mild hepatic impairment (Child-Pugh Score A) as a dose reduction of abacavir may be required. Abacavir/dolutegravir/lamivudine is contraindicated in moderate (Child-Pugh Score B) or severe (Child-Pugh Score C) hepatic impairment. • Elvitegravir: There were no clinically relevant differences in pharmacokinetics observed in mild (Child-Pugh Score A) or moderate (Child-Pugh Score B) hepatic impairment. Elvitegravir has not been studied in patients with severe hepatic impairment (Child-Pugh Score C) and is not recommended.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir.

Projected Place in Therapy

- The VHA Office of Public Health HIV Registry Reports indicates there were 26,784 HIV infected veterans in VHA care in 2013.
- **Abacavir/dolutegravir/lamivudine** is approved for use in the treatment of HIV-1 infections; this fixed-dose combination allows for one tablet once daily regimen that may improve patient adherence with antiretroviral therapy. Dolutegravir/abacavir/lamivudine is considered to be a DHHS recommended regimen for antiretroviral-naïve patients, however; it is not suitable for co-infected patients with Hepatitis B co-infection.
- **Elvitegravir** is approved for use in treatment-experienced HIV-1 infections in combination with a ritonavir boosted protease inhibitor and a second antiretroviral drug.

References

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.